Clinical trial results:
Open-label, Multicenter Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein, BIIB029, in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia B

Summary

EudraCT number	2011-003076-36
Trial protocol	GB IE NL
Global end of trial date	24 November 2014

Results information

Result version number	v1
This version publication date	05 February 2016
First version publication date	14 June 2015

Trial information

Trial identification

Sponsor protocol code	9HB02PED

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01440946
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000914-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the safety of rFIXFc in previously treated pediatric subjects with hemophilia B. Secondary objectives of this study in this study population are as follows: to evaluate the efficacy of rFIXFc for prevention and treatment of bleeding episodes; to evaluate and assess the PK of rFIXFc; to evaluate rFIXFc consumption for prevention and treatment of bleeding episodes.

Protection of trial subjects:

Only subjects who met the eligibility criteria were enrolled into the trial.

The first dose of rFIXFc was administered under medical supervision in the clinic and subjects were tested for inhibitor formation at screening and at each clinic visit prior to dosing. Medications and resuscitation equipment for the emergency management of anaphylactic reactions were available in the room where the subject's first injection was performed. In addition, the subject was provided with specific instructions by the Investigator on what to do if such an event occurred while at home, including how to seek emergency medical treatment.

In addition to scheduled clinic visits, at least one telephone call was planned midway between visits for study site staff to check on each subject’s status.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	30
EEA total number of subjects	11

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	29
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subject eligibility for the study was determined up to 8 weeks prior to the Baseline Visit. This period could be extended if the subject had a bleeding episode requiring factor IX (FIX) treatment within 5 days prior to the first dose of prestudy FIX. Some eligibility assessments were repeated for rescreened subjects with a >8-week screening window.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Subjects < 6 Years Old

Arm description:

At the Baseline visit (28 ± 7 days prior to Day 1), subjects received a single IV injection of prestudy FIX over 10 (±5) minutes in the clinic under medical supervision at a dose of 50 IU/kg. A washout period with no FIX treatment was required prior to administration of prestudy FIX and prior to rFIXFc. At Day 1, subjects received a single IV injection of rFIXFc over 10 (±5) minutes at a dose of 50 IU/kg. Immediately after the last PK sampling, the first prophylactic dose of approximately 50 to 60 IU/kg was administered in clinic as an IV injection.

Dose could be increased or decreased in increments of 10 IU/kg; increases to a maximum of 100 IU/kg and frequency of administration to a maximum of twice weekly, were allowed as indicated.

Arm type	Experimental
Investigational medicinal product name	rFIXFc
Investigational medicinal product code	rFIXFc
Other name	BIIB029, recombinant human coagulation factor IX Fc fusion protein, Alprolix
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff members were instructed to refer to the Directions for Handling and Administration (DHA) Manual located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Vials of rFIXFc were combined as needed, based on the actual labeled potency to achieve the subject's calculated dose. Partial vial use was allowed, in order to achieve the calculated dose.

Investigational medicinal product name	FIX
Investigational medicinal product code	
Other name	Factor IX
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff members were instructed to refer to the Directions for Handling and Administration (DHA) Manual located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Vials of prestudy FIX (provided by the subjects) were combined as needed, based on the nominal labeled potency (e.g., 250 IU, 500 IU, and 1000 IU), to achieve the subject's calculated dose.

Arm title	Subjects 6 to < 12 Years Old

Arm description:

At the Baseline visit (28 ± 7 days prior to Day 1), subjects received a single IV injection of prestudy FIX over 10 (±5) minutes in the clinic under medical supervision at a dose of 50 IU/kg. A washout period with no FIX treatment was required prior to administration of prestudy FIX and prior to rFIXFc. At Day 1, subjects received a single IV injection of rFIXFc over 10 (±5) minutes at a dose of 50 IU/kg. Immediately after the last PK sampling, the first prophylactic dose of approximately 50 to 60 IU/kg was administered in clinic as an IV injection.

Dose could be increased or decreased in increments of 10 IU/kg; increases to a maximum of 100 IU/kg and frequency of administration to a maximum of twice weekly, were allowed as indicated.

Arm type	Experimental
Investigational medicinal product name	rFIXFc
Investigational medicinal product code	rFIXFc
Other name	BIIB029, recombinant human coagulation factor IX Fc fusion protein, Alprolix
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff members were instructed to refer to the Directions for Handling and Administration (DHA) Manual located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Vials of rFIXFc were combined as needed, based on the actual labeled potency to achieve the subject's calculated dose. Partial vial use was allowed, in order to achieve the calculated dose.

Investigational medicinal product name	FIX
Investigational medicinal product code	
Other name	Factor IX
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff members were instructed to refer to the Directions for Handling and Administration (DHA) Manual located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Vials of prestudy FIX (provided by the subjects) were combined as needed, based on the nominal labeled potency (e.g., 250 IU, 500 IU, and 1000 IU), to achieve the subject's calculated dose.

Number of subjects in period 1	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old
Started	15	15
Completed	13	14
Not completed	2	1
Physician decision	1	-
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Subjects < 6 Years Old

Reporting group description:

At the Baseline visit (28 ± 7 days prior to Day 1), subjects received a single IV injection of prestudy FIX over 10 (±5) minutes in the clinic under medical supervision at a dose of 50 IU/kg. A washout period with no FIX treatment was required prior to administration of prestudy FIX and prior to rFIXFc. At Day 1, subjects received a single IV injection of rFIXFc over 10 (±5) minutes at a dose of 50 IU/kg. Immediately after the last PK sampling, the first prophylactic dose of approximately 50 to 60 IU/kg was administered in clinic as an IV injection.

Dose could be increased or decreased in increments of 10 IU/kg; increases to a maximum of 100 IU/kg and frequency of administration to a maximum of twice weekly, were allowed as indicated.

Reporting group title	Subjects 6 to < 12 Years Old

Reporting group description:

At the Baseline visit (28 ± 7 days prior to Day 1), subjects received a single IV injection of prestudy FIX over 10 (±5) minutes in the clinic under medical supervision at a dose of 50 IU/kg. A washout period with no FIX treatment was required prior to administration of prestudy FIX and prior to rFIXFc. At Day 1, subjects received a single IV injection of rFIXFc over 10 (±5) minutes at a dose of 50 IU/kg. Immediately after the last PK sampling, the first prophylactic dose of approximately 50 to 60 IU/kg was administered in clinic as an IV injection.

Dose could be increased or decreased in increments of 10 IU/kg; increases to a maximum of 100 IU/kg and frequency of administration to a maximum of twice weekly, were allowed as indicated.

Reporting group values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old	Total
Number of subjects	15	15	30
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	1	0	1
Children (2-11 years)	14	15	29
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	2.6	8.3	
standard deviation	± 0.99	± 1.45	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	15	15	30

Subject analysis sets

Subject analysis set title	All subjects
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects

Reporting group values	All subjects		
Number of subjects	30		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	1		
Children (2-11 years)	29		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	5.5		
standard deviation	± 3.16		
Gender categorical Units: Subjects			
Female	0		
Male	30		

End points

End points reporting groups

Reporting group title	Subjects < 6 Years Old

Reporting group description:

At the Baseline visit (28 ± 7 days prior to Day 1), subjects received a single IV injection of prestudy FIX over 10 (±5) minutes in the clinic under medical supervision at a dose of 50 IU/kg. A washout period with no FIX treatment was required prior to administration of prestudy FIX and prior to rFIXFc. At Day 1, subjects received a single IV injection of rFIXFc over 10 (±5) minutes at a dose of 50 IU/kg. Immediately after the last PK sampling, the first prophylactic dose of approximately 50 to 60 IU/kg was administered in clinic as an IV injection.

Dose could be increased or decreased in increments of 10 IU/kg; increases to a maximum of 100 IU/kg and frequency of administration to a maximum of twice weekly, were allowed as indicated.

Reporting group title	Subjects 6 to < 12 Years Old

Reporting group description:

At the Baseline visit (28 ± 7 days prior to Day 1), subjects received a single IV injection of prestudy FIX over 10 (±5) minutes in the clinic under medical supervision at a dose of 50 IU/kg. A washout period with no FIX treatment was required prior to administration of prestudy FIX and prior to rFIXFc. At Day 1, subjects received a single IV injection of rFIXFc over 10 (±5) minutes at a dose of 50 IU/kg. Immediately after the last PK sampling, the first prophylactic dose of approximately 50 to 60 IU/kg was administered in clinic as an IV injection.

Dose could be increased or decreased in increments of 10 IU/kg; increases to a maximum of 100 IU/kg and frequency of administration to a maximum of twice weekly, were allowed as indicated.

Subject analysis set title	All subjects
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects

Primary: Occurrence of Factor IX (FIX) Inhibitor Development

End point title	Occurrence of Factor IX (FIX) Inhibitor Development[1]

End point description:

An inhibitor test result ≥0.6 BU/mL, identified and confirmed by re-testing of a second sample obtained within 2 to 4 weeks, was considered positive. Both tests were to be performed using the Nijmegen-modified Bethesda Assay by the central laboratory. The incidence rates along with the 95% CI were summarized for all titers for subjects with 50 or more EDs to rFIXFc and a valid inhibitor test after the 50th exposure. In addition, the incidence rates for all subjects regardless of their EDs to rFIXFc were also summarized. The 95% CI was calculated using Clopper-Pearson exact method. Safety Analysis Set: subjects who received at least 1 dose of prestudy FIX, or at least 1 dose of rFIXFc; n=number of subjects with given number of EDs who had a valid inhibitor test.

End point type	Primary

End point timeframe:

Up to 50 weeks +/- 7 days, or up to 50 EDs if reached prior to Week 50

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The incidence of confirmed inhibitor formation from the central laboratory was summarized for each age cohort and a 95% CI was calculated for each incidence for this endpoint, as presented in this data table. No further statistical analyses were planned.

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old	All subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15[2]	15[3]	30[4]	
Units: percentage of subjects				
number (confidence interval 95%)				
Subjects with ≥ 50 EDs; n=10, 13, 23	0 (0 to 30.85)	0 (0 to 23.16)	0 (0 to 14.25)	
All subjects regardless of # of EDs; n=15, 15, 30	0 (0 to 21.8)	0 (0 to 21.8)	0 (0 to 11.57)	

Notes:

[2] - Safety Analysis Set; n=subjects with given number of exposure days who had a valid inhibitor test.

[3] - Safety Analysis Set; n=subjects with given number of exposure days who had a valid inhibitor test.

[4] - Safety Analysis Set; n=subjects with given number of exposure days who had a valid inhibitor test.

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate

End point title	Annualized Bleeding Rate

End point description:

Annualized bleeding rate=(number of bleeding episodes during the efficacy period/total number of days during the efficacy period)*365.25. Efficacy period begins with the first prophylactic dose of rFIXFc and ends with the last dose (for prophylaxis or a bleeding episode). Surgery/rehabilitation periods and PK evaluation periods are not included in the efficacy period. A bleeding episode started from the first sign of bleeding and ended ≤72 hours after the last treatment for the bleeding episode, within which any symptoms of bleeding at the same location or injections ≤72 hours apart were considered the same bleeding episode. Any injection to treat the bleeding episode taken >72 hours after the preceding 1 was considered the first injection to treat a new bleeding episode at the same location. Any bleeding at a different location was considered a separate bleeding episode, regardless of time from last injection. Full Analysis Set: subjects who received at least 1 dose of rFIXFc.

End point type	Secondary

End point timeframe:

Up to 50 weeks +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[5]	15[6]		
Units: bleeding episodes per participant per yr				
median (inter-quartile range (Q1-Q3))	1.09 (0 to 2.9)	2.13 (0 to 4.17)		

Notes:

[5] - Full Analysis Set; based on the number of subjects whose efficacy period was ≥ 1 day in duration.

[6] - Full Analysis Set; based on the number of subjects whose efficacy period was ≥ 1 day in duration.

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Joint Bleeding Rate (AJBR; Spontaneous)

End point title	Annualized Joint Bleeding Rate (AJBR; Spontaneous)

End point description:

AJBR for spontaneous joint bleeding episode=(number of bleeding episodes during the efficacy period/total number of days during the efficacy period)*365.25. Efficacy period begins with the first prophylactic dose of rFIXFc and ends with the last dose (for prophylaxis or a bleeding episode). Surgery/rehabilitation and PK evaluation periods are not included in the efficacy period. A bleeding episode started from the first sign of bleeding and ended ≤72 hours after the last treatment for the bleeding episode, within which any symptoms of bleeding at the same location or injections ≤72 hours apart were considered the same bleeding episode. Any injection to treat the bleeding episode taken >72 hours after the preceding 1 was considered the first injection to treat a new bleeding episode at the same location. Any bleeding at a different location was considered a separate bleeding episode, regardless of time from last injection. Full Analysis Set: subjects who received ≥ 1 dose of rFIXFc.

End point type	Secondary

End point timeframe:

Up to 50 weeks +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[7]	15[8]		
Units: bleeding episodes per participant per yr				
median (inter-quartile range (Q1-Q3))	0 (0 to 1.2)	0 (0 to 2.2)		

Notes:

[7] - Full Analysis Set; based on the number of subjects whose efficacy period was ≥1 day in duration.

[8] - Full Analysis Set; based on the number of subjects whose efficacy period was ≥1 day in duration.

Statistical analyses

No statistical analyses for this end point

Secondary: Subject Assessment of Response to Injections to Treat a Bleeding Episode

End point title	Subject Assessment of Response to Injections to Treat a Bleeding Episode

End point description:

Subject's assessment of the response (provided by the caregiver) to the first rFIXFc injection for each bleeding episode. Percentages were based on the number of bleeding episodes for which a response was provided for the first injection, using the following 4-point scale: excellent=abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection; good=definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an injection, but possibly requiring more than one injection after 24 to 48 hours for complete resolution; moderate=probable or slight beneficial effect within 8 hours after the initial injection and requiring more than one injection; no response=no improvement, or condition worsened, within approximately 8 hours after the initial injection. Full Analysis Set: subjects who received at least 1 dose of rFIXFc and had ≥ 1 bleeding episode; based on the number of injections with an evaluation.

End point type	Secondary

End point timeframe:

Up to 50 weeks +/- 7 days

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[9]	11[10]		
Units: percent of 1st injections w/ a response				
number (not applicable)				
Excellent or Good	89.5	88.2		
Excellent	52.6	41.2		
Good	36.8	47.1		
Moderate	5.3	11.8		
No Response	5.3	0		

Notes:

[9] - Full Analysis Set; percentages are based on the number of injections (total number of injections=19)

[10] - Full Analysis Set; percentages are based on the number of injections (total number of injections=34)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rFIXFc Consumption by Type of Injection

End point title	Annualized rFIXFc Consumption by Type of Injection

End point description:

Annualized consumption of rFIXFc for prevention of bleeding (prophylactic), treatment of bleeding, and other rFIXFc injections. Consumption is calculated for the efficacy period. The efficacy period began with the first prophylactic dose of rFIXFc and ended with the last dose (regardless of the reason for dosing). Surgery/rehabilitation and PK evaluation periods were not included in the efficacy period. Annualized consumption = (total IU/kg of study treatment received during the efficacy period / total number of days during the efficacy period)*365.25. Subjects who did not have a particular injection type are counted as having zero injections for that type.

End point type	Secondary

End point timeframe:

Up to 50 weeks +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[11]	15[12]		
Units: IU/kg rFIXFc per year				
arithmetic mean (standard deviation)				
Prophylactic injections	3041.5 (± 577.55)	3185.6 (± 683.71)		
Injections for bleeding	147.9 (± 209.89)	293.8 (± 515.59)		
Other injections	29.2 (± 48.93)	16.9 (± 44.9)		

Notes:

[11] - Full Analysis Set: subjects who received at least 1 dose of rFIXFc.

[12] - Full Analysis Set: subjects who received at least 1 dose of rFIXFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days From the Last Prophylaxis Injection to a Spontaneous Bleeding Episode

End point title	Number of Days From the Last Prophylaxis Injection to a Spontaneous Bleeding Episode

End point description:

The number of days from the last prophylaxis injection to the onset of a new spontaneous bleeding episode, analyzed across all evaluable bleeding episodes per subject and per episode, based on the efficacy period. Evaluable bleeding episodes are those for which both a date and time are available for both the onset of the bleeding episode and the previous prophylactic injection. The efficacy period begins with the first prophylactic dose of rFIXFc and ends with the last dose (for prophylaxis or a bleeding episode). Surgery/rehabilitation periods and PK evaluation periods are not included in the efficacy period. For 'Per subject' values, the number of days from the last prophylactic injection to a spontaneous bleeding episode is averaged across all evaluable spontaneous bleeding episodes per subject. Full Analysis Set: subjects who received at least 1 dose of rFIXFc; number of subjects and number of episodes were determined for subjects with at least 1 evaluable spontaneous episode.

End point type	Secondary

End point timeframe:

Up to 50 weeks +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[13]	6[14]		
Units: days				
median (inter-quartile range (Q1-Q3))				
Per spontaneous bleeding episode	3.97 (0.71 to 4.27)	5.55 (3.3 to 6.04)		
Per subject	4.12 (2.33 to 5.3)	5.52 (4.41 to 6.04)		

Notes:

[13] - Full Analysis Set; the number of evaluable spontaneous bleeding episodes analyzed was 5.

[14] - Full Analysis Set; the number of evaluable spontaneous bleeding episodes analyzed was 11.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections Required for Resolution of a Bleeding Episode

End point title	Number of Injections Required for Resolution of a Bleeding Episode

End point description:

The number of injections required to resolve a bleeding episode per subject and per episode, based on the efficacy period. The efficacy period begins with the first prophylactic dose of rFIXFc and ends with the last dose (for prophylaxis or a bleeding episode). Surgery/rehabilitation periods and PK evaluation periods are not included in the efficacy period. All injections given from the initial sign of a bleeding episode, until the last date/time within the bleeding episode window are counted. The resolution of a bleeding episode is defined as no sign of bleeding following injection for the bleeding episode. For 'Per subject' values, the number of injections required to resolve each bleeding episode is averaged across all bleeding episodes per subject. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc; number of subjects and number of episodes were determined for subjects with at least 1 evaluable bleeding episode.

End point type	Secondary

End point timeframe:

Up to 50 weeks +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[15]	11[16]		
Units: injections				
median (inter-quartile range (Q1-Q3))				
Per bleeding episode	1 (1 to 1)	1 (1 to 2)		
Per participant	1 (1 to 1.2)	1 (1 to 1.7)		

Notes:

[15] - Full Analysis Set; the number of bleeding episodes analyzed was 22.

[16] - Full Analysis Set; the number of bleeding episodes analyzed was 38.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose Required for Resolution of a Bleeding Episode

End point title	Total Dose Required for Resolution of a Bleeding Episode

End point description:

The total dose required to resolve a bleeding episode per subject and per episode, based on the efficacy period. The efficacy period begins with the first prophylactic dose of rFIXFc and ends with the last dose (for prophylaxis or a bleeding episode). Surgery/rehabilitation periods and PK evaluation periods are not included in the efficacy period. For 'Per bleeding episode' values, for each bleeding episode, the total dose is the sum of the doses (IU/kg) administered across all injections given to treat that bleeding episode. For 'Per subject' values, the total dose (IU/kg) used to resolve each bleeding episode is averaged across all bleeding episodes per subject. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc; number of subjects and number of episodes were determined for subjects who had complete information on the dose administered to treat a bleeding episode.

End point type	Secondary

End point timeframe:

Up to 50 weeks +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[17]	11[18]		
Units: injections				
median (inter-quartile range (Q1-Q3))				
Per bleeding episode	65.37 (50.68 to 125)	89.77 (50.92 to 140.86)		
Per subject	70.22 (55.4 to 97.22)	52.22 (27.03 to 161.06)		

Notes:

[17] - Full Analysis Set; the number of bleeding episodes analyzed was 22.

[18] - Full Analysis Set; the number of bleeding episodes analyzed was 38.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Activity (Cmax; One-stage Activated Partial Thromboplastin Time [aPTT] Clotting Assay)

End point title	Maximum Plasma Activity (Cmax; One-stage Activated Partial Thromboplastin Time [aPTT] Clotting Assay)

End point description:

Cmax: maximum plasma FIX activity during a dosing interval. The values for Cmax were adjusted to the nominal dose of 50 IU/kg. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: all subjects with adequate PK data, defined as complete and evaluable PK samples through 168 hours after rFIXFc dosing. Complete means the availability of the 168-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28±7 days before Day 1) Prestudy FIX Dosing: predose; 30±5 min, 3 hrs±30 min, 10±2 hrs, 24±3 hrs, 48±4 hrs postdose. Day 1 rFIXFc Dosing: predose; 30±5 min, 3 hrs ±30 min, 10±2 hrs, 24±3 hrs, 72±7 hrs, 120±12 hrs, 168±16 hrs postdose.

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11[19]	13[20]		
Units: IU/dL				
geometric mean (confidence interval 95%)	29.78 (26.18 to 33.87)	35.84 (30.56 to 42.03)		

Notes:

[19] - All subjects in the PK subgroup with adequate PK data

[20] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half Life (t1/2; One-stage aPTT Clotting Assay)

End point title	Terminal Half Life (t1/2; One-stage aPTT Clotting Assay)

End point description:

t1/2: time required for the concentration of the drug to reach half of its original value in the body. Non-compartmental methods. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: all subjects with adequate PK data, defined as complete and evaluable PK samples through 168 hours after rFIXFc dosing. Complete means the availability of the 168-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28±7 days before Day 1) Prestudy FIX Dosing: predose; 30±5 min, 3 hrs±30 min, 10±2 hrs, 24±3 hrs, 48±4 hrs postdose. Day 1 rFIXFc Dosing: predose; 30±5 min, 3 hrs ±30 min, 10±2 hrs, 24±3 hrs, 72±7 hrs, 120±12 hrs, 168±16 hrs postdose.

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11[21]	13[22]		
Units: hours				
geometric mean (confidence interval 95%)	66.49 (55.86 to 79.14)	70.34 (60.95 to 81.17)		

Notes:

[21] - All subjects in the PK subgroup with adequate PK data

[22] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL; One-stage aPTT Clotting Assay)

End point title	Clearance (CL; One-stage aPTT Clotting Assay)

End point description:

CL: the measure of the efficiency of the body to remove the drug and the unit is the volume of the plasma or blood cleared of drug per unit time. Non-compartmental methods. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: all subjects with adequate PK data, defined as complete and evaluable PK samples through 168 hours after rFIXFc dosing. Complete means the availability of the 168-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28±7 days before Day 1) Prestudy FIX Dosing: predose; 30±5 min, 3 hrs±30 min, 10±2 hrs, 24±3 hrs, 48±4 hrs postdose. Day 1 rFIXFc Dosing: predose; 30±5 min, 3 hrs ±30 min, 10±2 hrs, 24±3 hrs, 72±7 hrs, 120±12 hrs, 168±16 hrs postdose.

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11[23]	13[24]		
Units: mL/h/kg				
geometric mean (confidence interval 95%)	4.365 (3.901 to 4.885)	3.505 (3.006 to 4.087)		

Notes:

[23] - All subjects in the PK subgroup with adequate PK data

[24] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss; One-stage aPTT Clotting Assay)

End point title	Volume of Distribution at Steady State (Vss; One-stage aPTT Clotting Assay)

End point description:

Vss: volume of distribution at steady state. Non-compartmental methods. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: all subjects with adequate PK data, defined as complete and evaluable PK samples through 168 hours after rFIXFc dosing. Complete means the availability of the 168-hour sample and at least enough other

samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28±7 days before Day 1) Prestudy FIX Dosing: predose; 30±5 min, 3 hrs±30 min, 10±2 hrs, 24±3 hrs, 48±4 hrs postdose. Day 1 rFIXFc Dosing: predose; 30±5 min, 3 hrs ±30 min, 10±2 hrs, 24±3 hrs, 72±7 hrs, 120±12 hrs, 168±16 hrs postdose.

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11[25]	13[26]		
Units: mL/kg				
geometric mean (confidence interval 95%)	365.1 (316.2 to 421.6)	289 (236.7 to 352.9)		

Notes:

[25] - All subjects in the PK subgroup with adequate PK data

[26] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Normalized Area Under the Curve (DNAUC; One-stage aPTT Clotting Assay)

End point title	Dose Normalized Area Under the Curve (DNAUC; One-stage aPTT Clotting Assay)

End point description:

DNAUC: dose normalized area under the drug concentration-time curve (extent of unmetabolized drug in circulation). Non-compartmental methods. The 95% confidence interval on the geometric mean is based on the t-statistic backtransformed from the log scale. PK Analysis Set: all subjects with adequate PK data, defined as complete and evaluable PK samples through 168 hours after rFIXFc dosing. Complete means the availability of the 168-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28±7 days before Day 1) Prestudy FIX Dosing: predose; 30±5 min, 3 hrs±30 min, 10±2 hrs, 24±3 hrs, 48±4 hrs postdose. Day 1 rFIXFc Dosing: predose; 30±5 min, 3 hrs ±30 min, 10±2 hrs, 24±3 hrs, 72±7 hrs, 120±12 hrs, 168±16 hrs postdose.

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11[27]	13[28]		
Units: IU*h/dL per IU/kg				
geometric mean (confidence interval 95%)	22.71 (20.32 to 25.38)	28.53 (24.47 to 33.27)		

Notes:

[27] - All subjects in the PK subgroup with adequate PK data

[28] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT; One-stage aPTT Clotting Assay)

End point title	Mean Residence Time (MRT; One-stage aPTT Clotting Assay)

End point description:

MRT: the average time for all the drug molecules to reside in the body. Non-compartmental methods. The 95% confidence interval on the geometric mean is based on the t-statistic backtransformed from the log scale. PK Analysis Set: all subjects with adequate PK data, defined as complete and evaluable PK samples through 168 hours after rFIXFc dosing. Complete means the availability of the 168-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28±7 days before Day 1) Prestudy FIX Dosing: predose; 30±5 min, 3 hrs±30 min, 10±2 hrs, 24±3 hrs, 48±4 hrs postdose. Day 1 rFIXFc Dosing: predose; 30±5 min, 3 hrs ±30 min, 10±2 hrs, 24±3 hrs, 72±7 hrs, 120±12 hrs, 168±16 hrs postdose.

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11[29]	13[30]		
Units: hours				
geometric mean (confidence interval 95%)	83.65 (71.76 to 97.51)	82.46 (72.65 to 93.6)		

Notes:

[29] - All subjects in the PK subgroup with adequate PK data

[30] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery (IR; One-stage aPTT Clotting Assay)

End point title	Incremental Recovery (IR; One-stage aPTT Clotting Assay)

End point description:

IR for FIX activity following rFIXFc dosing: IU/dL rise in plasma FIX per IU/kg drug administered. Non-compartmental methods. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale.PK Analysis Set: all subjects with adequate PK data, defined as complete and evaluable PK samples through 168 hours after rFIXFc dosing. Complete means the availability of the 168-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28±7 days before Day 1) Prestudy FIX Dosing: predose; 30±5 min, 3 hrs±30 min, 10±2 hrs, 24±3 hrs, 48±4 hrs postdose. Day 1 rFIXFc Dosing: predose; 30±5 min, 3 hrs ±30 min, 10±2 hrs, 24±3 hrs, 72±7 hrs, 120±12 hrs, 168±16 hrs postdose.

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11[31]	13[32]		
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)	0.5898 (0.5152 to 0.6752)	0.717 (0.6115 to 0.8407)		

Notes:

[31] - All subjects in the PK subgroup with adequate PK data

[32] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment of the Subject's Response to His rFIXFc Regimen

End point title	Physician's Global Assessment of the Subject's Response to His rFIXFc Regimen

End point description:

Investigators assessed each subject's response to his rFIXFc regimen using a 4-point scale: excellent=bleeding episodes responded to ≤ the usual number of injections or ≤ the usual dose of rFIXFc or the rate of breakthrough bleeding during prophylaxis was ≤ that usually observed; effective=most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, or there was a minor increase in the rate of breakthrough bleeding; partially effective=bleeding episodes most often required more injections and/or higher doses than expected, or adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses; ineffective=routine failure to control hemostasis, or hemostatic control required additional agents. Percentages are based on the total number of responses; multiple responses per subject are counted. Full Analysis Set: subjects who received ≥ 1 dose of rFIXFc.

End point type	Secondary

End point timeframe:

Up to 50 weeks +/- 7 days

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[33]	15[34]		
Units: percentage of responses				
number (not applicable)				
Excellent	85.4	89.8		
Effective	14.6	10.2		
Partially Effective	0	0		
Ineffective	0	0		

Notes:

[33] - percentages based on the number of responses (n=48)

[34] - percentages are based on the number of responses (n=59)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (AEs): from informed consent up to 21 days after last dose; AEs: from Baseline (28 ± 7 days prior to Day 1) up to 14 (+7) days after last dose.

Adverse event reporting additional description:

Length of rFIXFc dosing was up to 50 weeks ± 7 days. Serious and non-serious AEs that were treatment-emergent with respect to rFIXFc are presented for those subjects in the Safety Analysis Set who were treated with rFIXFc.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Subjects < 6 Years Old

Reporting group description:

At the Baseline visit (28 ± 7 days prior to Day 1), subjects received a single IV injection of prestudy FIX over 10 (±5) minutes in the clinic under medical supervision at a dose of 50 IU/kg. A washout period with no FIX treatment was required prior to administration of prestudy FIX and prior to rFIXFc. At Day 1, subjects received a single IV injection of rFIXFc over 10 (±5) minutes at a dose of 50 IU/kg. Immediately after the last PK sampling, the first prophylactic dose of approximately 50 to 60 IU/kg was administered in clinic as an IV injection.

Dose could be increased or decreased in increments of 10 IU/kg; increases to a maximum of 100 IU/kg and frequency of administration to a maximum of twice weekly, were allowed as indicated.

Reporting group title	Subjects 6 to < 12 Years Old

Reporting group description:

At the Baseline visit (28 ± 7 days prior to Day 1), subjects received a single IV injection of prestudy FIX over 10 (±5) minutes in the clinic under medical supervision at a dose of 50 IU/kg. A washout period with no FIX treatment was required prior to administration of prestudy FIX and prior to rFIXFc. At Day 1, subjects received a single IV injection of rFIXFc over 10 (±5) minutes at a dose of 50 IU/kg. Immediately after the last PK sampling, the first prophylactic dose of approximately 50 to 60 IU/kg was administered in clinic as an IV injection.

Dose could be increased or decreased in increments of 10 IU/kg; increases to a maximum of 100 IU/kg and frequency of administration to a maximum of twice weekly, were allowed as indicated.

Serious adverse events	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)	1 / 15 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Device occlusion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 15 (80.00%)	14 / 15 (93.33%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	4 / 15 (26.67%)	0 / 15 (0.00%)	
occurrences (all)	7	0	
Immune system disorders			
Seasonal allergy			

subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Cough			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Upper-airway cough syndrome			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Accidental drug intake by child			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Bite			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Excoriation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Face injury			
subjects affected / exposed	2 / 15 (13.33%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Fall			

subjects affected / exposed	2 / 15 (13.33%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Head injury			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	2	
Joint injury			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Limb injury			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Lip injury			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Traumatic haematoma			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	3	
Tremor			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Iron deficiency anaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Cheilitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Dental caries			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Duodenal ulcer			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Faeces discoloured			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Haematochezia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vomiting			

subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Eczema			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Rash maculo-papular			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
Croup infectious			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Ear infection			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	6	0	
Fungal skin infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Gastroenteritis viral			

subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Impetigo			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nail infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	6 / 15 (40.00%)	
occurrences (all)	1	8	
Oral bacterial infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Pharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Upper respiratory tract infection			

bacterial			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Varicella			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	4 / 15 (26.67%)	0 / 15 (0.00%)	
occurrences (all)	4	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Food intolerance			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2013	The primary reasons for this amendment were as follows: - Added interim PK analyses. Data from the interim PK analyses were used to support marketing authorization in specific countries (e.g., United States) for individuals under the age of 12. In addition, the PK data were used to inform the design of a clinical study in previously untreated patients (PUPs) that is required by the EU. - Increased the sample size from at least 20 subjects to approximately 26 subjects to be dosed to ensure at least 10 subjects per cohort completed the study. - Recategorized endpoints for patient-reported and health utilization outcomes from secondary endpoints to exploratory endpoints, and notified that these will be analyzed in a separate report.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported